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<p>(21) International Application Number: PCT/US97/12335</p> <p>(22) International Filing Date: 15 July 1997 (15.07.97)</p> <p>(30) Priority Data: 60/012,727 15 July 1996 (15.07.96) US</p> <p>(71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</p> <p>(72) Inventors: GALE, Robert, M.; 1276 Russel Avenue, Los Altos, CA 94024 (US). NELSON, Melinda, K.; 1127 Hollenback Road, Sunnyvale, CA 94087-2403 (US). CORMIER, Michel, J., N.; 278 Andsbury Avenue, Mountain View, CA 94043 (US). GUPTA, Suneel, K.; 1331 Elsona Drive, Sunnyvale, CA 94087 (US). CAMPBELL, Patricia, S.; 1410 Middlefield Road, Palo Alto, CA 94301-3350 (US).</p> <p>(74) Agents: RAFA, Michael, J. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: NOVEL FORMULATIONS FOR THE ADMINISTRATION OF FLUOXETINE</p> <p>(57) Abstract</p> <p>Composition of matter for application to a body surface or membrane to administer fluoxetine by permeation through the body surface or membrane, the composition comprising fluoxetine to be administered, at a therapeutically effective rate, alone or in combination with a permeation enhancer or mixture. A preferred embodiment is directed to the transdermal administration of fluoxetine at reduced skin irritation levels wherein fluoxetine, preferably provided as fluoxetine acetate, is coadministered with a corticosteroid such as hydrocortisone. Also disclosed are drug delivery devices containing the fluoxetine or fluoxetine and enhancer composition and methods for the transdermal administration of the fluoxetine and fluoxetine/enhancer composition.</p>		

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1 NOVEL FORMULATIONS FOR
2 THE ADMINISTRATION OF FLUOXETINE

3
4 FIELD OF INVENTION

5
6 This invention relates to sustained release formulations for the
7 safe and efficacious administration of fluoxetine for, among other things,
8 the treatment of depression. More particularly, the invention relates to
9 novel methods, compositions, and devices for transdermally administering
10 fluoxetine to a subject through a body surface or membrane over a sustained
11 time period. A preferred embodiment is directed to the transdermal
12 administration of fluoxetine at reduced skin irritation levels.

13
14 BACKGROUND OF THE INVENTION

15
16 Fluoxetine, (\pm)-N-methyl- γ -[4-(trifluoromethyl)-phenoxy]
17 benzenepropanamine, is one of the 3-aryloxy-3-phenylpropylamine
18 compounds described in US Patent No. 4,314,081. Additionally,
19 U.S. Patent No. 4,626,549 discloses a method of blocking the uptake of
20 monoamines such as serotonin by brain neurons in animals comprising
21 administering a "monoamine blocking amount" of a 3-aryloxy-3-
22 phenylpropylamine compound, such as fluoxetine. It is a potent, highly
23 selective reuptake inhibitor of serotonin (5-hydroxytryptamine) and is
24 indicated for the treatment of depression and obsessions and compulsions
25 related to obsessive-compulsive disorder (OCD). As an antidepressant or
26 for the treatment of OCD, fluoxetine is administered orally as a solution or in
27 tablets as fluoxetine hydrochloride (Prozac ®) in 10 mg or 20 mg daily doses
28 and has an elimination half-life of from 1 - 9 days, averaging about 2-3 days.
29 Other methods for the production of fluoxetine and new intermediates are
30 disclosed in U.S. Patent No. 5,225,585.

1 Fluoxetine is a racemic mixture (50/50) of R-fluoxetine and S-fluoxetine
2 enantiomers. The delivery of the S(+) enantiomer is disclosed in the prior art.
3 For example, U.S. Patent No. 5,104,899 discloses a method of treating
4 depression in a human patient comprising administering the S(+) enantiomer
5 of fluoxetine in substantially optically pure form. PCT application WO
6 95/28152 discloses methods for treating or improving memory, and for
7 treating sexual dysfunction, while avoiding the unwanted adverse toxic or
8 psychological effects associated with the racemic mixture of fluoxetine,
9 comprising administering a therapeutically effective amount of S(+) fluoxetine
10 or a pharmaceutically acceptable salt thereof, substantially free of its R(-)
11 stereoisomer.

12 The use of fluoxetine for indications other than treating depression
13 is also disclosed in the following: U.S. Patent Nos. 4,594,358, 4,647,591,
14 4,683,235, 4,940,585, 4,999,382, 5,151,448, 5,356,934, 5,446,070,
15 5,589,511, and PCT Application WO 92/18005. Transdermal delivery as
16 a route of administering fluoxetine is mentioned in these patents, though
17 specific formulations or delivery regimens are nowhere disclosed. Other uses
18 of fluoxetine are disclosed in U.S. Patent Nos. 4,035,511, 4,083,982,
19 4,329,356, 4,444,778, 4,590,213, 4,895,845, and 5,589,512, all of which
20 do not disclose the transdermal administration route.

21 Additionally, US Patent No. 5,601,839 discloses transdermal
22 formulations for enhancing dermal penetration of a basic drug, including
23 fluoxetine, comprising a matrix formulation comprising an amount of the basic
24 drug and a permeation enhancer consisting essentially of triacetin in a
25 polymer layer, preferably a pressure sensitive adhesive.

26 The oral administration of fluoxetine in the treatment of depression
27 is initiated with a 20 mg/day dose administered in the morning. If no
28 improvement is observed over several weeks, the dosage may be increased,
29 though not to exceed 80 mg/day. Doses above 20 mg/day should be

1 administered once a day in the morning or by a b.i.d. schedule (morning and
2 noon).

3 The transdermal route of parenteral delivery of drugs and other
4 biologically active agents ("agents") has been proposed for a wide variety of
5 systemically acting and locally acting agents on either a rate-controlled or
6 non-rate-controlled basis and is described in numerous technical publications
7 such as the following: US Patents 3,598,122; 3,598,123; 3,731,683;
8 3,797,494; 4,031,894; 4,201,211; 4,286,592; 4,314,557; 4,379,454;
9 4,435,180; 4,559,222; 4,573,995; 4,588,580; 4,645,502; 4,704,282;
10 4,788,062; 4,816,258; 4,849,226; 4,904,475; 4,908,027; 4,938,759;
11 4,943,435; 5,004,610; 5,122,382; 5,141,750; 5,314,694; and 5,342,623.

12 When first investigated in depth in the late 1960's, the transdermal
13 route of administration appeared to offer many advantages, particularly with
14 respect to agents that had short half lives and therefore required frequent,
15 repeated dosing or were subject to a high degree of first-pass metabolism by
16 the liver when orally administered. The peaks and valleys in blood
17 concentration resulting from frequent periodic doses of short half-life agents
18 would be eliminated and replaced by substantially constant plasma
19 concentration. This would not only improve individual compliance but also
20 would eliminate the alternating periods of high side-effects and ineffective
21 blood concentrations associated with period dosing. Administering the agent
22 through the skin directly into the blood stream would also eliminate first-pass
23 metabolism of orally administered agents.

24 It was initially assumed, theoretically, that any short half-life agent of
25 high potency and skin permeability would be suitable for safe and effective
26 transdermal administration. This assumption, however, has not been proven
27 true.

28 The failure of the transdermal route to fulfill the initial expectations of
29 its potential as an administrative portal was primarily due to the incredible
30 variety of properties with which nature has endowed the skin to permit it to

1 perform its function as the primary barrier to prevent the ingress of foreign
2 substances into the body. See Transdermal Drug Delivery: Problems and
3 Possibilities, B. M. Knepp, et al, CRC Critical Reviews and Therapeutic Drug
4 Carrier Systems, Vol. 4, Issue 1 (1987) and Transdermal Delivery Systems:
5 A Medical Rationale, Gary W. Cleary, Topical Drug Bioavailability,
6 Bioequivalence, and Penetration, Plenum Press, 1993.

7 Thus, the transdermal route of administration, rather than being
8 available to every short half-life agent of high potency and skin permeability,
9 was found to be available only to those few agents that possess the proper
10 combination of a host of characteristics, most of which are unpredictable,
11 required to render the agent suitable for safe and effective transdermal
12 administration.

13 The most significant of these characteristics are the following:

14 1. Skin Permeability. The permeability of the skin to the agent
15 must be sufficiently high so that the agent can be administered at a
16 therapeutically effective rate through an area of skin no greater than about
17 200 cm² and preferably no greater than 50 cm². The person-to-person
18 variation in skin permeability at similar sites should also be considered.
19 U.S. Patent Nos. 4,568,343, 4,746,515, 4,863,738, 4,865,848, 4,888,354,
20 5,378,730, 5,641,504 and WO 95/09006, WO 95/01167, WO 96/37231, and
21 WO 96/40259 are related to various compositions and methods for enhancing
22 permeation of drugs through the skin.

23 2. Skin Binding. The skin beneath the transdermal delivery device
24 has the capability of creating a skin depot of drug by absorbing, adsorbing, or
25 binding a certain amount of agent. The amount of agent so bound must be
26 supplied to the skin before the agent can be delivered into the blood stream
27 at steady, therapeutically effective rates. If large amounts of the agent are
28 bound in the skin, significant delays in the onset of therapeutic effect ("lag
29 time") will be observed together with corresponding delays and termination

1 of effect upon removal of the device. The potential also exists for toxic
2 quantities of potent agents to be contained within the skin beneath the device.
3 Skin binding is not related to skin permeability. Agents that are highly
4 permeable may also be highly bound causing a lag time sufficiently long as
5 to render them unsuitable for their intended use.

6 3. Irritation. The skin reacts to many topically applied substances,
7 particularly those maintained under occlusion, by blistering or reddening
8 accompanied by unpleasant burning, itching, and stinging sensations.
9 Animal models are used to screen for irritation. Animal models, however,
10 often produce both false positives and false negatives. There is also a
11 wide interpersonal variation in susceptibility to irritation. An agent must be
12 minimally irritating in a large percentage of the potential individual population
13 in order to be suitable for safe and effective transdermal administration.
14 U.S. Patent Nos. 4,552,872, 4,756,710, 5,028,431, 5,130,139, 5,160,741,
15 and 5,451,407 are directed to overcoming problems associated with skin
16 irritation associated with transdermal drug delivery.

17 4. Sensitization. Sensitization is an allergic reaction which is
18 induced when an agent is first applied to the skin and is elicited upon
19 continued exposure which may occur immediately or after a long period of
20 seemingly harmless exposure.

21 The sensitization may be local, elicited by topical exposure,
22 which manifests itself as contact dermatitis accompanied by blistering,
23 itching, reddening and burning at the site of application. More seriously,
24 the sensitization may be systemic, elicited by topical application but
25 manifesting itself by more general allergic reactions at sites other than
26 the site of application. Most seriously, the systemic sensitization may be
27 elicited by oral or intravenous administration of the drug. If the latter occurs,
28 the individual will be unable to take the drug by any route of administration.

1 Animal models are used to screen for sensitization. Animal models,
2 however, produce both false positives and false negatives. There is also a
3 wide variation in the allergic reaction between individuals as well as between
4 sexes, races and skin types. It is obvious that a useful transdermal agent
5 must be minimally sensitizing in a large percentage of the potential individual
6 population. U.S. Patent Nos. 5,000,956, 5,049,387, 5,120,145, and 5,149,539
7 are directed to overcoming sensitization problems associated with
8 transdermal drug delivery by the coadministration of a corticosteroid.

9 5. Pharmacokinetic Properties. The half-life of an agent is the time
10 after administration that half of the amount administered has been eliminated
11 from the body. Because blood concentrations of continuously administered
12 agents will continue to increase for approximately five half-lives before
13 steady-state constant blood concentrations are achieved, an agent must have
14 a relatively short half-life to be suitable for continuous transdermal
15 administration. The transdermal half-lives of most agents have not been
16 determined. When half-lives of agents determined from intravenous
17 administration are compared with half-lives determined from transdermal
18 administration, the transdermal half-lives are generally longer but there can
19 be wide variation in half-life between individuals based upon factors such as
20 age, sex, health, and body type.

21 6. Pharmacodynamic Properties. Constant blood levels may not
22 produce the desired therapeutic effects. For example, a therapeutic effect
23 may only be observed at peak blood concentration obtained from bolus
24 dosing but the peak blood or plasma concentration cannot be maintained
25 because of side effects associated therewith. Also, continuous administration
26 of many agents produces tolerance that may require either some agent-free
27 interval or continually increasing and therefore potentially hazardous doses of
28 the agent.

1 7. Potency. Although a certain degree of potency is required for
2 transdermally administered agent to be effective, it is also possible for an
3 agent to be too potent. As potency increases, lower blood concentrations are
4 required and much smaller quantities are administered. Because of normal
5 inter-individual variations and skin permeability, it may not be possible to
6 precisely control whether a individual is receiving 1 $\mu\text{g/hr}$ or 2 $\mu\text{g/hr}$, for
7 example. For a highly potent agent, a 1 $\mu\text{g/hr}$ administration may be totally
8 ineffective and a 2 $\mu\text{g/hr}$ rate fatal. Thus, the therapeutic index of an agent,
9 which is the ratio of toxic blood concentration to the therapeutic blood
10 concentration, becomes extremely significant. A highly potent agent should
11 also have a relatively wide therapeutic window in order to be suitable for
12 transdermal administration.

13 8. Metabolism. One of the perceived advantages of transdermal
14 administration was that it avoided the "first-pass" metabolism of the agent by
15 the liver that is associated with oral administration. It has now been
16 recognized, however, that the skin is also a large metabolizing organ in the
17 body for some drugs. Thus, although first-pass metabolism that occurs after
18 an orally administered agent enters the blood stream can be avoided, skin
19 metabolism, which occurs before the agent enters the bloodstream, cannot
20 be avoided. Skin metabolism is capable of creating metabolites that are inert,
21 irritating, toxic, or comparable in biological activity to that of the agent. An
22 agent, to be suitable for transdermal administration, must have the metabolic
23 properties that are consistent with its therapeutic use on continuous
24 administration.

25 The above summarizes the primary characteristics that effect suitability
26 of an agent for transdermal administration that have been recognized to date.

27 There are undoubtedly others, some of which have not yet been recognized,
28 and, in order for an agent to be suitable for transdermal administration, it must
29 possess the right combination of all these characteristics, a combination of
30 which, as illustrated by the very few drugs that are now suitable for

1 administration from transdermal delivery devices, is quite rare and
2 unpredictable.

3

4

DESCRIPTION OF TERMS

5

6 As used herein, the term "bioequivalents" intends that there is greater
7 than 90% probability that the bioavailability is 80 - 125% and the minimum
8 and maximum blood or plasma concentrations are 80 - 125% of the
9 referenced dose.

10 As used herein, the term "fluoxetine" intends not only the basic form
11 of fluoxetine but also pharmaceutically acceptable salt forms of fluoxetine,
12 the R or S enantiomers of fluoxetine, either individually or as a racemic
13 mixture, and to mixtures thereof.

14 As used herein, the term "fluoxetine therapy" intends all medical
15 conditions for which fluoxetine is or will be indicated, including, without
16 limitation, for the treatment of depression and obsessive-compulsive disorder.

17 As used herein, the term "individual" intends a living mammal and
18 includes, without limitation, humans and other primates, livestock and sports
19 animals such as cattle, pigs and horses, and pets such as cats and dogs.

20 As used herein, the term "irritation-reducing amount" intends an
21 amount of an anti-irritant which reduces skin irritation throughout a substantial
22 portion of the administration period.

23 As used herein, the term "permeation enhancement" intends an
24 increase in the permeability of skin to fluoxetine and/or anti-irritant in the
25 presence of a permeation enhancer as compared to permeability of skin
26 to fluoxetine and/or anti-irritant in the absence of a permeation enhancer.

27 As used herein, the term "permeation enhancer" intends an agent
28 or a mixture of agents which acts to increase the permeability of the skin
29 to fluoxetine and/or anti-irritant.

1 As used herein, the term "permeation-enhancing amount" intends an
2 amount of a permeation enhancer which provides permeation enhancement
3 throughout a substantial portion of the administration period.

4 As used herein, the phrase "predetermined area of skin" intends a
5 defined area of intact unbroken skin or mucosal tissue. That area will usually
6 be in the range of about 5 cm² to about 100 cm².

7 As used herein the term "salt" intends, but is not limited to,
8 pharmaceutically acceptable organic or inorganic salts. Typical inorganic
9 salts include hydrogen halides such as hydrochlorides, carbonates,
10 phosphates, sulfates, hydrogen sulfates, hydrobromides, nitrates, and
11 sulfides. Organic salts includes, but are not limited to, acid addition salts
12 including salts of monocarboxylic and polycarboxylic acids such as the
13 acetate, maleate, and citrate.

14 As used herein, the phrase "sustained time period" or "administration
15 period" intends at least about 8 hours and will typically intend a period in the
16 range of about one to about seven days.

17 As used herein, the term "therapeutically effective amount" intends the
18 dose of fluoxetine and/or its active metabolite, norfluoxetine, that provides
19 fluoxetine therapy, in the case of adult and juvenile humans, the optimum
20 dosage range is the equivalent of the oral dose of about 5 - 80 mg fluoxetine
21 per day.

22 As used herein, the term "therapeutically effective rate" intends a rate
23 of fluoxetine and/or its active metabolite, norfluoxetine, delivery effective to
24 achieve therapeutic blood or plasma levels in an individual during the
25 administration period and is typically within the range of 250 - 3200 µg/hr.

26 As used herein, the term "therapeutic blood or plasma level" intends
27 the level of fluoxetine and/or its active metabolite, norfluoxetine, in blood or
28 plasma that achieves a therapeutic effect for the desired fluoxetine therapy.

1 As used herein, the term "transdermal" intends both percutaneous and
2 transmucosal administration, i.e., passage of fluoxetine through intact
3 unbroken skin or mucosal tissue into the systemic circulation.

4

5 SUMMARY OF THE INVENTION

6

7 One aspect of this invention is directed to a method of transdermally
8 administering a drug having a relatively long half-life.

9 Another aspect of this invention is provide sustained release
10 formulations to administer a therapeutically effective amount of fluoxetine
11 and/or its active metabolite, norfluoxetine, over an administration period.

12 More specifically, it is an aspect of this invention to provide
13 compositions and methods for the transdermal delivery of fluoxetine and/or its
14 active metabolites, and delivery systems for effecting the same, which are
15 suitable for the transdermal administration of fluoxetine and/or its active
16 metabolites continuously through a body surface or membrane at a
17 therapeutically effective rate in order to achieve and maintain therapeutic
18 blood or plasma levels in an individual.

19 Another aspect of this invention is to provide compositions, devices,
20 and methods for transdermally administering fluoxetine at reduced skin
21 irritation levels.

22 Another aspect of this invention is to improve patient compliance of
23 patients in need of fluoxetine therapy by providing compositions, devices, and
24 methods for the transdermal administration of fluoxetine at a therapeutically
25 effective rate.

26 Yet another aspect of this invention is directed to compositions,
27 devices, and methods for the transdermal administration of fluoxetine at
28 reduced skin irritation levels together with a suitable permeation enhancer.

1 According to this invention, it has been discovered that fluoxetine can
2 be safely and efficaciously administered transdermally at a therapeutically
3 effective rate to provide, among other things, treatment for depression, when
4 administered alone or when coadministered with a suitable permeation
5 enhancer. A preferred embodiment is directed to transdermally administering
6 a therapeutically effective amount of fluoxetine at reduced skin irritation levels
7 wherein fluoxetine is coadministered from a transdermal drug delivery device
8 containing a pharmaceutically acceptable salt of fluoxetine, an anti-irritant,
9 and a permeation enhancer in order to provide systemic administration of
10 fluoxetine.

11 These and other aspects of the present invention will be readily
12 apparent from the description and accompanying figures that follow.

13

14

BRIEF DESCRIPTION OF THE FIGURES

15

16 Figure 1 is a cross-section through a schematic perspective view of
17 one embodiment of a transdermal therapeutic system according to this
18 invention.

19 Figure 2 is a cross-section view through another embodiment of this
20 invention prior to application to the skin.

21 Figure 3 is a cross-section view through another embodiment of this
22 invention prior to application to the skin.

23 Figure 4 is a cross-section view through another embodiment of this
24 invention prior to application to the skin.

25 Figure 5 is a graph depicting the flux of fluoxetine base through
26 epidermis from oil/petrolatum formulations with varying amounts of GML.

27 Figure 6 is a graph depicting the flux of fluoxetine base through
28 epidermis from oil/petrolatum formulations with varying amounts of methyl
29 laurate.

1 Figure 7 is a graph depicting the flux of fluoxetine base through
2 epidermis from oil/petrolatum formulations with varying amounts of GML and
3 5% methyl laurate.

4 Figure 8 is a graph depicting the flux of fluoxetine acetate through
5 epidermis from EVA systems with various permeation enhancers.

6 Figure 9 is a graph depicting the flux of hydrocortisone through
7 epidermis from EVA systems containing fluoxetine acetate with various
8 permeation enhancers.

9 Figure 10 is a graph depicting fluoxetine and norfluoxetine plasma
10 concentrations.

11

12 DETAILED DESCRIPTION OF THE INVENTION

13

14 One aspect of the invention is directed to a method of transdermal
15 administration of an agent having a relatively long half-life, i.e. greater than
16 about 24 hours. Previously, only agents having short half-lives were
17 considered as suitable for transdermal administration. However, the present
18 inventors have found that agents having such long half-lives may be
19 advantageous for transdermal administration in that periodic missed doses
20 would not be as likely to produce a fall in plasma drug levels below the
21 minimum therapeutic blood or plasma level. Thus, it may be preferable to
22 administer such drugs from a transdermal system which is placed onto the
23 skin and maintained in drug transmitting relation for a first predetermined
24 period of time and then replaced after a lapse of a second predetermined
25 period of time of up to about 4 days. The first predetermined period of time
26 is within 24 - 168 hours, preferably about 48 - 120 hours. The second
27 predetermined period of time is within about 20 - 100 hours, preferably
28 about 30 - 90 hours.

1 In addition to providing therapeutic blood or plasma levels for the
2 period in which the device is applied to the skin, administration according to
3 this embodiment is effective to maintain therapeutic blood or plasma levels of
4 the agent in the patient throughout the period in which the system is not in
5 drug transmitting relation with the skin of the patient. Although such a delivery
6 regimen applies to any agent having the necessary half-life and therapeutic
7 window, it will be described according to a preferred embodiment for
8 delivering fluoxetine.

9 For example, one embodiment is directed to a system which contains
10 an amount of fluoxetine effective to deliver fluoxetine at a therapeutically
11 effective rate for approximately 3 days. The system would be worn for
12 approximately three days and yet provide effective fluoxetine therapy
13 throughout at least five days due to fluoxetine's long half-life. It is believed
14 that such treatment regimens could improve patient compliance, particularly
15 in individuals on maintenance therapy to prevent recurrent depression where
16 fluoxetine therapy may be required for periods of five years or more.

17 To determine the administration regimen, an administration rate is
18 determined by the relation:

$$19 \qquad \qquad \qquad \text{administration rate} = CL \cdot C_{ss} \qquad (1)$$

20 where CL is the clearance and C_{ss} is the steady state concentration of
21 the drug.

22
23 The 90% steady state plasma concentration is the plateau
24 concentration achieved by constant drug administration and is achieved by
25 constant administration for approximately 3 to 4 half-lives of the drug. For
26 example, a drug having a half life of 24 hours will have to be administered at
27 a constant rate for approximately 4 days to reach 90% steady state. The drug
28 concentration may be expressed in relation to the steady state concentration
29 and the half life of the drug by the following expression:

30

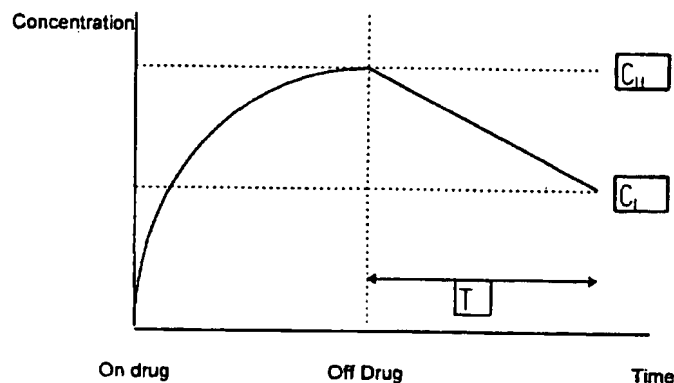
$$C = C_{ss} [1 - (1/2)^n] \quad (2)$$

where n = the number of half-lives elapsed since initiation of constant drug delivery.

Assuming that the drug input is stopped after achieving the upper limit of the therapeutic window, the time T it takes for the plasma concentration to drop to the lower limit of the therapeutic window is given by the following relation:

$$T = t_{1/2} / 0.693 \cdot \ln C_U / C_L \quad (3)$$

wherein T = time for drug plasma concentration to drop from upper therapeutic window limit C_U to its lower therapeutic window limit C_L . This relationship is shown in the Concentration vs. Time schematic below.



Thus, a steady state concentration is selected such that the resulting value for C derived by Equation (2) is within the therapeutic window for the drug and is sufficiently high to remain within the window throughout the period of no drug administration. The steady state concentration may be determined by one of ordinary skill in the art provided with values for drug clearance, half life, and therapeutic window.

1 For example, assuming a fluoxetine half-life of 48 hours, in order to
2 maintain fluoxetine levels of 15 - 55 ng/mL, T is determined by equation (2)
3 to be 90 hours. Thus, after achieving levels of 55 ng/mL, a system could then
4 be removed while maintaining therapeutic levels for roughly 3.75 days. In the
5 preferred embodiment directed to the administration of fluoxetine, the first
6 predetermined period is preferably about 60 - 120 hours and the second
7 predetermined period is preferably about 36 - 80 hours.

8 Examples of drugs having relatively long half-lives suitable for
9 administration by this regimen include, but are not limited to, amiloride,
10 amiodarone, amitriptyline, chloroquine, chlorpheniramine, chlorpromazine,
11 chlorpropamide, chlorthalidone, clonazepam, dapsone, desipramine,
12 nordazepam, diazepam, diazoxide, digitoxin, digoxin, doxepin, doxorubicin,
13 doxycycline, ethosuximide, fluoxetine, flurazepam, furosemide, haloperidol,
14 imipramine, nitrazepam, norfluoxetine, nortriptyline, paroxetine,
15 phenylbutazone, phenytoin, pimozide, piroxicam, protriptyline, and warfarin.

16 In another aspect of this invention, it has been discovered that
17 fluoxetine can be safely and efficaciously administered by a sustained release
18 formulation. More specifically, it has been found that fluoxetine can be safely
19 and efficaciously administered transdermally at a therapeutically effective rate
20 to provide, among other things, treatment for depression, when administered
21 alone or coadministered with a suitable permeation enhancer. The present
22 invention provides novel compositions, devices, and methods for fluoxetine
23 therapy with improved patient compliance to an individual in need of such
24 therapy.

25 The present inventors have found that fluoxetine is moderately to
26 severely irritating when administered transdermally as the base. A preferred
27 embodiment of the present invention is therefore directed to providing
28 compositions, devices, and methods for the transdermal administration
29 of fluoxetine at reduced skin irritation levels. According to this preferred
30 embodiment, a pharmaceutically acceptable salt of fluoxetine is

1 coadministered with an anti-irritant, preferably a corticosteroid such as
2 hydrocortisone. Particularly surprising is the discovery by the present
3 inventors that a pharmaceutically acceptable salt of fluoxetine can be
4 coadministered at therapeutically effective rates together with an anti-irritant
5 and optionally, a permeation enhancer, from a single transdermal device in
6 order to transdermally administer fluoxetine at reduced skin irritation levels
7 throughout the administration period.

8 A particularly preferred embodiment is directed to the transdermal
9 administration of fluoxetine acetate as the inventors have found that
10 fluoxetine acetate may be transdermally administered at therapeutically
11 effective rates and at reduced irritation levels without the use of permeation
12 enhancers. Fluoxetine maleate is another preferred salt according to this
13 invention but requires coadministration with a suitable permeation enhancer.
14 Other salts which provide the necessary flux and irritation levels can be
15 determined in accordance with the principles of the teachings of this
16 invention.

17 Therapeutic blood or plasma levels can be obtained from
18 administration rates in the range of 250 - 3200 $\mu\text{g/hr}$. Representative
19 *in vitro* skin fluxes of fluoxetine through human skin are in the range of about
20 7 - 120 $\mu\text{g/cm}^2 \cdot \text{hr}$, depending on the drug form, permeation enhancer, and if
21 an in-line adhesive is present.

22 The range of desired and achievable cumulative release of fluoxetine,
23 arriving through the skin at a limited area is equivalent to the oral dosage
24 of 10 - 80 mg per 24 hours. The system is easily adapted to provide a
25 cumulative release of fluoxetine over a 24 hour period of less than 10 mg
26 if necessary. Additionally, the system is easily adapted for shorter
27 or longer duration treatments.

28 The desired fluoxetine administration rate may be achieved by
29 increasing the surface area of the transdermal delivery device without
30 increasing the flux. For example, for a fluoxetine skin flux of approximately

1 20 $\mu\text{g}/\text{cm}^2 \cdot \text{hr}$, the surface area of a patch would have to have a surface area
2 of about 40 cm^2 in order to deliver approximately 19 mg of fluoxetine over a
3 24 hour period. The flux of fluoxetine through skin may also be increased by
4 the use of permeation enhancers discussed below. A preferred embodiment
5 of this invention relates to codelivery of a permeation enhancer to assist in the
6 transdermal administration of fluoxetine and/or anti-irritant.

7 This invention finds particular usefulness in administering fluoxetine
8 across skin. It is also useful, however, in administering fluoxetine across
9 mucosa. According to the invention, fluoxetine is placed in fluoxetine
10 transmitting relationship to an appropriate body surface, preferably in a
11 pharmaceutically acceptable carrier thereof, and maintained in place for
12 the desired administration period.

13 The fluoxetine, anti-irritant, and/or permeation enhancer, if used, are
14 typically dispersed within a physiologically compatible matrix or carrier, as
15 more fully described below, which may be applied directly to the body as an
16 ointment, gel, cream, suppository or sublingual or buccal tablet. When used
17 in the form of a liquid, ointment, lotion, cream or gel applied directly to the
18 skin, it is preferable, although not required, to occlude the site of
19 administration. Such compositions can also contain other permeation
20 enhancers, stabilizers, dyes, diluents, pigments, vehicles, inert fillers,
21 excipients, gelling agents, vasoconstrictors, and other components of topical
22 compositions as are known to the art.

23 In other embodiments, fluoxetine would be administered from a
24 transdermal delivery device as more fully described below. Examples of
25 suitable transdermal delivery devices are illustrated in Figs. 1 - 4. In the
26 figures, the same reference numbers are used throughout the different figures
27 to designate the same or similar components. The figures are not drawn to
28 scale.

1 Referring now to Figure 1, a preferred embodiment of a transdermal
2 therapeutic system according to this invention comprises transdermal delivery
3 device 10 comprising a reservoir 12, preferably in the form of a matrix
4 containing fluoxetine, anti-irritant, and a permeation enhancer dispersed
5 therein. Reservoir 12 is sandwiched between a backing 14 and an in-line
6 contact adhesive layer 16. The device 10 adheres to the surface of the skin
7 18 by means of the adhesive layer 16. The adhesive layer 16 may optionally
8 contain the permeation enhancer, anti-irritant, and/or fluoxetine. A strippable
9 release liner (not shown in FIG. 1) is normally provided along the exposed
10 surface of adhesive layer 16 and is removed prior to application of device
11 10 to the skin 18. Optionally, a rate-controlling membrane (not shown) may
12 be present between the reservoir 12 and the adhesive layer 16. Additionally,
13 a non-rate controlling tie layer membrane as disclosed in U.S. Patent
14 No. 5,635,203, may be present between the reservoir 12 and adhesive 16
15 in any of the embodiments depicted in figures 1- 4.

16 Although the preferred embodiments of this invention utilize an in-line
17 adhesive as is shown in Figure 1, other means for maintaining the system on
18 the skin can be employed. Such means include a peripheral ring of adhesive
19 outside the path of the drug from the system to the skin or the use of other
20 fastening means such as buckles, belts, and elastic arm bands.

21 Alternatively, reservoir 12 may be in the form of a matrix containing
22 fluoxetine, anti-irritant, and permeation enhancer, if used, dispersed within a
23 suitable adhesive, preferably a pressure sensitive adhesive. Such pressure
24 sensitive adhesives include, but are not limited to, polysiloxanes,
25 polyacrylates, polyurethanes, acrylic adhesives including cross linked or
26 uncross linked acrylic copolymers, vinyl acetate adhesives, ethylene
27 vinylacetate copolymers, and natural or synthetic rubbers including
28 polybutadienes, polyisoprenes, and polyisobutylene adhesives, and mixtures
29 and graft copolymers thereof. The matrix formulations according to this
30 embodiment comprise the adhesive containing fluoxetine, anti-irritant, and

1 permeation enhancer, if present, laminated to a backing on one surface and
2 to a release liner on the other. In addition to the fluoxetine, anti-irritant, and
3 permeation enhancer, the matrix or carrier may also contain dyes, pigments,
4 inert fillers, excipients and other conventional components of pharmaceutical
5 products or transdermal devices known to the art. For example, the matrix
6 may also be provided with hydrophilic water absorbing polymers known in the
7 art such as polyvinyl alcohol and polyvinyl pyrrolidone individually or in
8 combination.

9 Alternatively, as shown in FIG. 2, transdermal therapeutic device 20
10 may be attached to the skin or mucosa of a patient by means of an adhesive
11 overlay 22. Device 20 is comprised of reservoir 12 preferably in the form of a
12 matrix containing fluoxetine, anti-irritant, and a permeation enhancer
13 dispersed therein. A backing layer 14 is provided adjacent one surface of
14 reservoir 12. Adhesive overlay 22 maintains the device on the skin and may
15 be fabricated together with, or provided separately from, the remaining
16 elements of the device. With certain formulations, the adhesive overlay 22
17 may be preferable to the in-line contact adhesive 16 as shown in FIG. 1.
18 Backing layer 14 is preferably slightly larger than reservoir 12, and in this
19 manner prevents the materials in reservoir 12 from adversely interacting with
20 the adhesive in overlay 22. Optionally, a rate-controlling membrane (not
21 shown in FIG. 2) may be provided on the skin-proximal side of reservoir 12.
22 A strippable release liner 24 is also provided with device 20 and is removed
23 just prior to application of device 20 to the skin.

24 In FIG. 3, transdermal delivery device 30 comprises a fluoxetine,
25 anti-irritant, and permeation enhancer reservoir ("fluoxetine reservoir")
26 12 substantially as described with respect to FIG. 1. Permeation enhancer
27 reservoir ("enhancer reservoir") 26 comprises the permeation enhancer
28 dispersed throughout and contains fluoxetine at or below saturation, when
29 in equilibrium with the fluoxetine reservoir 12. Enhancer reservoir 26 is
30 preferably made from substantially the same matrix as is used to form

1 fluoxetine reservoir 12. A rate-controlling membrane 28 for controlling the
2 release rate of the permeation enhancer from enhancer reservoir 26 to
3 fluoxetine reservoir 12 is placed between the two reservoirs. A rate-
4 controlling membrane (not shown in FIG. 3) for controlling the release rate of
5 the enhancer, anti-irritant, and/or fluoxetine from fluoxetine reservoir 12 to the
6 skin may also optionally be utilized and would be present between adhesive
7 layer 16 and reservoir 12.

8 The rate-controlling membrane may be fabricated from permeable,
9 semipermeable or microporous materials which are known in the art to control
10 the rate of agents into and out of delivery devices and having a permeability
11 to the permeation enhancer lower than that of drug reservoir 12. Suitable
12 materials include, but are not limited to, polyethylene, polyvinyl acetate,
13 ethylene n-butyl acetate and ethylene vinyl acetate copolymers.

14 Superimposed over the permeation enhancer reservoir 26 of device 30
15 is a backing 14. On the skin-proximal side of reservoir 12 are an adhesive
16 layer 16 and a strippable liner 24 which would be removed prior to application
17 of the device 30 to the skin.

18 In the embodiments of FIGS. 1, 2 and 3, the carrier or matrix material
19 of the reservoirs has sufficient viscosity to maintain its shape without oozing
20 or flowing. If, however, the matrix or carrier is a low-viscosity flowable
21 material such as a liquid or a gel, the composition can be fully enclosed in a
22 pouch or pocket, as known to the art from US Pat. No. 4,379,454 (noted
23 above), for example, and as illustrated in FIG. 4. Device 40 shown in FIG. 4
24 comprises a backing member 14 which serves as a protective cover for the
25 device, imparts structural support, and substantially keeps components in
26 device 40 from escaping the device. Device 40 also includes reservoir 12,
27 which contains the fluoxetine and any anti-irritant and/or permeation enhancer
28 and bears on its surface distant from backing member 14, a rate-controlling
29 membrane 28 for controlling the release of fluoxetine, anti-irritant, and/or

1 permeation enhancer from device 40. The outer edges of backing member
2 14 overlay the edges of reservoir 12 and are joined along the perimeter
3 with the outer edges of the rate-controlling membrane 28 in a fluid-tight
4 arrangement. This sealed reservoir may be effected by pressure, fusion,
5 adhesion, an adhesive applied to the edges, or other methods known in
6 the art. In this manner, reservoir 12 is contained wholly between backing
7 member 14 and rate-controlling membrane 28. On the skin-proximal side
8 of rate-controlling membrane 28 are an adhesive layer 16 and a strippable
9 liner 24 which would be removed prior to application of the device 40 to
10 the skin.

11 In an alternative embodiment of device 40 of FIG. 4, reservoir 12
12 contains the permeation enhancer and anti-irritant and contains fluoxetine at
13 or below saturation. The fluoxetine and an additional amount of permeation
14 enhancer and/or anti-irritant are present in adhesive layer 16, which acts as
15 a separate reservoir.

16 Fluoxetine can be administered to human skin or mucosa by direct
17 application to the skin or mucosa in the form of an ointment, gel, cream or
18 lotion, for example, but are preferably administered from a skin patch or other
19 known transdermal delivery device which contains a saturated or unsaturated
20 formulation of the fluoxetine and any anti-irritant and/or enhancer. The
21 formulation may be aqueous or non-aqueous based. The formulation should
22 be designed to deliver the fluoxetine and any anti-irritant and/or enhancer at
23 the necessary fluxes. Aqueous formulations typically comprise water or
24 water/ethanol and about 1-5 wt% of a gelling agent, an example being a
25 hydrophilic polymer such as hydroxyethylcellulose or hydroxypropylcellulose.
26 Typical non-aqueous gels are comprised of silicone fluid or mineral oil.
27 Mineral oil-based gels also typically contain 1-2 wt% of a gelling agent such
28 as colloidal silicon dioxide. The suitability of a particular gel depends upon
29 the compatibility of its constituents with the fluoxetine, anti-irritant, and the

1 permeation enhancer, if used, in addition to any other components in the
2 formulation.

3 The reservoir matrix should be compatible with fluoxetine, the
4 permeation enhancer, and any carrier therefor. The term "matrix" as used
5 herein refers to a well-mixed composite of ingredients. When using an
6 aqueous-based formulation, the reservoir matrix is preferably a hydrophilic
7 polymer, e.g., a hydrogel.

8 When using a non-aqueous based formulation, the reservoir matrix is
9 preferably composed of a hydrophobic polymer. Suitable polymeric matrices
10 are well known in the transdermal drug delivery art, and examples are listed
11 in the above-named patents. A typical laminated system would consist
12 essentially of a polymeric membrane and/or matrix such as ethylene vinyl
13 acetate (EVA) copolymers, such as those described in U.S. Pat. No.
14 4,144,317, preferably having a vinyl acetate (VA) content in the range of
15 from about 9% up to about 60% and more preferably about 9% to 40% VA.
16 Polyisobutylene/oil polymers containing from 4-25% high molecular weight
17 polyisobutylene and 20-81% low molecular weight polyisobutylene with the
18 balance being an oil such as mineral oil or polybutene may also be used as
19 the matrix material.

20 The amount of fluoxetine present in the therapeutic device and
21 required to achieve an effective therapeutic result depends on many factors,
22 such as the minimum necessary dosage of the fluoxetine for the particular
23 indication being treated; the solubility and permeability of the matrix, taking
24 into account the presence of an anti-irritant, permeation enhancer, of the
25 adhesive layer and of the rate-controlling membrane, if present; and the
26 period of time for which the device will be fixed to the skin. The minimum
27 amount of fluoxetine is determined by the requirement that sufficient
28 quantities of fluoxetine must be present in the device to maintain the desired
29 rate of release over the given period of application. The maximum amount

1 for safety purposes is determined by the requirement that the quantity of
2 fluoxetine present cannot exceed a rate of release that reaches toxic levels.

3 The fluoxetine may be present in the matrix or carrier at a
4 concentration at or below saturation. An excess amount of fluoxetine above
5 saturation may be included in the matrix or carrier, the amount of excess
6 being a function of the desired length of the delivery period of the system.
7 Fluoxetine may be present at a level below saturation without departing from
8 this invention as long as it is continuously administered to the skin or mucosal
9 site at a therapeutic rate and for a period of time sufficient to deliver a
10 therapeutically effective amount of fluoxetine that provides the desired
11 therapeutic result.

12 The permeation enhancer useful in the present invention is selected
13 from those compounds which are compatible with fluoxetine and which
14 provide enhanced skin permeation to the drug when it is administered
15 together with the drug to the skin of a user. Additionally, the permeation
16 enhancer must not adversely interact with the adhesive of the in-line contact
17 adhesive layer if one is present. Examples of permeation enhancers are
18 disclosed in the patents cited above and can be selected from, but are not
19 limited to, fatty acids, monoglycerides of fatty acids such as glycerol
20 monolaurate, glycerol monooleate or glycerol monolinoleate; lactate esters of
21 fatty acids such as lauryl lactate, cetyl lactate, and myristyl lactate; acyl
22 lactylates such as caproyl lactic acid; lauramide diethanolamine (LDEA);
23 esters of fatty acids having from about 10 to about 20 carbon atoms including
24 lauryl acetate; alkyl laurates such as methyl laurate; dimethyl lauramide;
25 isopropyl myristate; polyethylene glycol-4 lauryl ether (Laureth-4);
26 polyethylene glycol monolaurate; and lower C₁₋₄ alcohols such as isopropanol
27 and ethanol, alone or in combinations of one or more.

28 A preferred permeation enhancer according to this invention comprises
29 a monoglyceride of a fatty acid together with a suitable cosolvent, including,
30 but not limited to, fatty acids esters such as lauryl lactate, lauryl acetate, and

1 methyl laurate. Methyl laurate has been found to be particularly desirable as
2 it is obtainable at a high degree of purity, thus providing a purer and better
3 defined permeation enhancer and a system which is more readily
4 characterized. According to a particularly preferred embodiment, the
5 permeation enhancer comprises glycerol monolaurate (GML) and methyl
6 laurate within the range of 1-25 wt% and 1-20 wt%, respectively, at a ratio
7 of GML/methyl laurate within the range of 0.5 - 5.0, preferably 1.0 - 3.5.

8 The permeation-enhancing mixture is dispersed through the matrix
9 or carrier, preferably at a concentration sufficient to provide permeation-
10 enhancing amounts of enhancer in the reservoir throughout the anticipated
11 administration period. Where there is an additional, separate permeation
12 enhancer matrix layer as well, as in FIGS. 3 and 4, the permeation enhancer
13 normally is present in the separate reservoir in excess of saturation.

14 The anti-irritant is dispersed throughout the matrix or carrier, preferably
15 at a concentration sufficient to deliver anti-irritant to the skin in an amount
16 effective to reduce skin irritation throughout the anticipated administration
17 period. The anti-irritant is preferably present in excess of saturation in order
18 to provide that the anti-irritant is continuously administered with the fluoxetine
19 and continues to be present as long as any fluoxetine is present in the
20 epidermis. Suitable anti-irritants include, but are not limited to, methyl
21 nicotinate as disclosed in U.S. Patent No. 5,451,407, corticosteroids, and
22 buffering agents including ascorbic acid and acetic acid. Such anti-irritants
23 are known in the art as seen in the above cited patents.

24 According to a preferred embodiment, the anti-irritant is a corticosteroid
25 and is preferably administered at a flux within the range of 0.1 - 5.0 $\mu\text{g}/\text{cm}^2$
26 hr. Hydrocortisone is the preferred corticosteroid. The total amount of
27 hydrocortisone administered is not to exceed 5 mg / 24 hour in order to avoid
28 possible systemic effects. Hydrocortisone esters such as hydrocortisone
29 acetate are also suitable. More potent corticosteroids may not require a
30 permeation enhancer as hydrocortisone and hydrocortisone acetate do.

1 However, the advantages of hydrocortisone or its esters such as
2 hydrocortisone acetate is that they are approved for over-the-counter use.
3 This invention contemplates the use of any corticosteroid in addition to
4 hydrocortisone and includes, without limitation, beclomethasone,
5 betamethasone, benzoid, betamethasone dipropionate, betamethasone
6 valerate, clobetasol propionate, clobetasol butyrate, desonide,
7 dexamethasone, fluocinonide, prednisolone, and triamcinolone, for example.

8 Because of the wide variation in skin permeability from individual to
9 individual and from site to site on the same body, it may be preferable that
10 the fluoxetine, anti-irritant, and/or permeation enhancer, be administered
11 from a rate-controlled transdermal delivery device. Rate control can be
12 obtained either through a rate-controlling membrane as described in
13 U.S. Patent No. 3,797,494 listed above, or through an adhesive or both as
14 well as through other means known in the art.

15 A certain amount of fluoxetine will bind reversibly to the skin, and it is
16 accordingly preferred that the skin-contacting layer of the device include this
17 amount of fluoxetine as a loading dose.

18 The surface area of the device of this invention can vary from about
19 1-200 cm². A typical device, however, will have a surface area within the
20 range of about 5-60 cm², preferably about 20 cm².

21 The devices of this invention can be designed to effectively deliver
22 fluoxetine for an extended time period of from several hours up to 7 days or
23 longer. Seven days is generally the maximum time limit for application of a
24 single device because the adverse affect of occlusion of a skin site increases
25 with time and the normal cycle of sloughing and replacement of the skin cells
26 occurs in about 7 days.

27 Preferably, a device for the transdermal administration of fluoxetine,
28 at a therapeutically effective rate, comprises:

- 1 (a) a reservoir comprising:
2 (i) 1-50% by weight fluoxetine,
3 (ii) 0.01 to 10% by weight anti-irritant,
4 (iii) 30 to 90% by weight of a polymeric carrier;
5 (b) a backing behind the skin-distal surface of the reservoir; and
6 (c) means for maintaining the reservoir in fluoxetine - transmitting
7 relation with the skin.

8 More preferably, a device for the transdermal administration of
9 fluoxetine, at a therapeutically effective rate, comprises:

- 10 (a) a reservoir comprising:
11 (i) 1 - 50% by weight of a pharmaceutically acceptable salt
12 of fluoxetine,
13 (ii) 0.01 to 10% by weight anti-irritant,
14 (iii) 1 - 50% by weight of a permeation enhancer,
15 (iv) 30 - 90% by weight of a polymeric carrier;
16 (b) a backing behind the skin-distal surface of the reservoir; and
17 (c) means for maintaining the reservoir in fluoxetine- transmitting
18 relation with the skin.

19 Most preferably, a device for the transdermal administration of
20 fluoxetine, at a therapeutically effective rate, comprises:

- 21 (a) a reservoir comprising:
22 (i) 10 - 50% by weight of a pharmaceutically acceptable salt
23 of fluoxetine,
24 (ii) 0.1 to 10% by weight corticosteroid,
25 (iii) 10 - 50% by weight of a permeation enhancer,
26 (iv) 30 - 90% by weight of a polymeric carrier;
27 (b) a backing behind the skin-distal surface of the reservoir; and
28 (c) means for maintaining the reservoir in fluoxetine, corticosteroid,
29 and permeation enhancer- transmitting relation with the skin.

1 The backing may be flexible or nonflexible and may be a breathable or
2 occlusive material. Suitable materials include, without limitation,
3 polyethylene, polyurethane, polyester, ethylene vinyl acetate, acrylonitrile,
4 cellophane, cellulose acetate, cellulose, ethylcellulose, ethylene vinyl
5 alcohol, plasticized vinylacetate-vinylchloride copolymers, polyethylene
6 terephthalate, nylons, rayon, polypropylene, polyvinyl alcohol, polyvinyl
7 chloride, metalized polyester films, polyvinylidene chloride, polycarbonate,
8 polystyrene, and aluminum foil. The backing may be a multi-laminate film.

9 The means for maintaining the reservoir in drug and permeation
10 enhancer transmitting relation with the skin is preferably a pressure sensitive
11 adhesive including, but not limited to, polyisobutylene adhesives, silicone
12 adhesives, and acrylate adhesives known in the art including copolymers and
13 graft copolymers thereof. A further embodiment of the invention is directed
14 to including in the adhesive a small percentage, e.g., from about 1 to about
15 5 wt% of fluoxetine to assure an appropriate initial release rate.

16 The aforementioned patents describe a wide variety of materials which
17 can be used for fabricating various layers or components of the transdermal
18 fluoxetine delivery systems according to this invention. This invention,
19 therefore, contemplates the use of other materials other than those
20 specifically disclosed herein including those which may become hereafter
21 known to the artist capable of forming the necessary functions.

22 The invention is also directed to a method of continuously
23 administering fluoxetine and/or norfluoxetine to a patient at a therapeutically
24 effective rate over an administration period in order to administer a
25 therapeutically effective amount and achieve and maintain therapeutic blood
26 or plasma levels in a patient.

27 Another method of the present invention is directed to a method
28 for the transdermal coadministration of fluoxetine and/or norfluoxetine at a
29 therapeutically effective rate together with an irritation reducing amount of an

1 anti-irritant in order to achieve and maintain therapeutic blood or plasma
2 levels in a patient, comprising:

3 (a) coadministering to a body surface or membrane, fluoxetine
4 and/or norfluoxetine; and

5 (b) an anti-irritant, wherein a therapeutically effective amount of
6 fluoxetine is delivered at a therapeutically effective rate during an
7 administration period in order to achieve and maintain therapeutic blood or
8 plasma levels in a patient. The fluoxetine and anti-irritant may be
9 administered to the body surface or membrane by means of the devices and
10 compositions described above.

11 A preferred embodiment of the present invention comprises a method
12 of treating depression. To achieve this result, fluoxetine is delivered at a
13 therapeutic rate within a range of about 250 - 3200 $\mu\text{g/hr}$, preferably at about
14 400-1200 $\mu\text{g/hr}$ from a reasonably sized transdermal delivery device having a
15 surface area of less than about 60 cm^2 for the treatment period, usually about
16 12 hours to 5 days.

17 The length of time of fluoxetine presence and the total amount of
18 fluoxetine in the plasma can be changed following the teachings of this
19 invention to provide different treatment regimens. Thus, they can be
20 controlled by the amount of time during which exogenous fluoxetine is
21 delivered transdermally to an individual or animal and the rate at which it is
22 administered.

23 Having thus generally described our invention, the following specific
24 examples describe preferred embodiments thereof but are not intended to
25 limit the invention in any manner.

26

27

EXAMPLE 1

28

29 Several test samples were made to measure the flux of fluoxetine base
30 through human cadaver epidermis from donor vehicles containing 10% by

1 weight fluoxetine base in an oil/petrolatum carrier with 0 - 10% by weight
2 glycerol monolaurate (GML) as shown in Table 1.

3 Table 1

4 Non-Aqueous Donor Solutions (weight percent)

Symbol (Fig. 5)	Fluoxetine	GML	Oil/Petrolatum
■	10	0	90
●	10	2.5	87.5
Δ	10	5	85
□	10	10	80

5
6 The experiment was carried out using standard glass diffusion cells
7 which consist of a donor compartment with a 7.5 ml capacity, and a receptor
8 compartment with a 22 ml capacity. A circular piece of epidermis was placed
9 in each diffusion cell (permeation area = 2.27 cm²) in a horizontal position
10 between a lower capped receptor compartment and an upper capped donor
11 compartment. The receptor compartment has both a venting tube (uncapped)
12 and a sampling port (capped). The stratum corneum side of the epidermis
13 faced the donor compartment. An O-ring was positioned between the
14 epidermis and the donor compartment, and a clamp held the compartments
15 together. The receptor solution, 22 ml of 0.001 M phosphoric acid solution,
16 pH 3.2, was added to each receptor compartment. The cells were placed in
17 a temperature controlled water bath shaker at 35°C and allowed to come to
18 temperature before the donor solution was added.

19 At each time interval, the receptor solution was removed from the test
20 cell and replaced with an equal volume of fresh receptor solution previously
21 equilibrated at 35°C. The receptor solutions for each time interval were then
22 assayed for fluoxetine by HPLC (Metachem Inertsil, ODS3, 15 cm x 2.0 mm
23 ID, 5 μm, Mobile phase: 35% acetonitrile / 64.25% water, 0.50%
24 triethylamine, 0.25% H₃PO₄ (85%), 244 nm, 0.3 ml/min) to calculate the

1 permeation rate of fluoxetine through epidermis from the donor solutions.
2 From the drug concentration and the volume of the receptor solutions, the
3 area of permeation and the time interval, the flux of the drug through the
4 epidermis was calculated as follows: (drug concentration X volume of
5 receptor)/(area x time) = flux ($\mu\text{g}/\text{cm}^2 \cdot \text{hr}$).

6 Figure 5 graphically depicts the results. As seen in Figure 5,
7 the average baseline skin flux of fluoxetine base without any permeation
8 enhancer is approximately $20 \mu\text{g}/\text{cm}^2 \cdot \text{hr}$ over a seventy two hour period.
9 The addition of GML acted to increase the fluoxetine flux from two to five fold.

10

11

EXAMPLE 2

12

13 Several test samples were made to measure the flux of fluoxetine
14 base through human cadaver epidermis from donor vehicles containing 10%
15 by weight fluoxetine base in an oil/petrolatum carrier with 0 - 10% by weight
16 methyl laurate (ML) as shown in Table 2. Transdermal fluxes were obtained
17 using human epidermis at 35°C in standard diffusion cells using the
18 procedure set forth in Example 1. Figure 6 graphically depicts the results.
19 As seen in Figure 6, methyl laurate by itself did not significantly increase the
20 fluoxetine flux.

21

TABLE 2

22

Non-Aqueous Donor Solutions (weight percent)

Symbol (Fig. 6)	Fluoxetine	ML	Oil/Petrolatum
■	10	0	90
●	10	2.5	87.5
Δ	10	5	85
□	10	10	80

23

EXAMPLE 3

Several test samples were made to measure the flux of fluoxetine base through human cadaver epidermis from donor vehicles containing 10% by weight fluoxetine base in an oil/petrolatum carrier with 5% by weight methyl laurate (ML) and 0 - 10% by weight GML as shown in Table 3. Transdermal fluxes were obtained using human epidermis at 35°C in standard diffusion cells using the procedure set forth in Example 1. As seen in Figure 7, the combination of methyl laurate and GML exhibited a synergistic effect on the flux of fluoxetine as compared to the enhancement of flux in the presence of GML or methyl laurate individually.

TABLE 3
Non-Aqueous Donor Solutions (weight percent)

Symbol (Fig. 7)	Fluoxetine	GML	ML	Oil/Petrolatum
■	10	0	5	85
●	10	2.5	5	82.5
Δ	10	5	5	80
□	10	10	5	75

EXAMPLE 4

Fluoxetine irritation and flux were studied in hairless guinea pigs. Formulations containing 30% (vol/vol) ethanol, 45% (vol/vol) propylene glycol, water, and fluoxetine base and acetate at various concentrations (%wt/vol) as shown in Table 4 were mixed together with ³H fluoxetine at a final concentration of 24μCi/mL and gelled with 4% methylcellulose.

Skin sites on hairless guinea pigs were lightly washed. 2 cm² systems were filled with 350 μL of the gel formulation. One radioactive gel and one placebo gel (no drug) was applied to each guinea pig on opposite sides of the animal (n=3 per group) and an adhesive overlay was placed over each

1 system. The guinea pigs were wrapped with Vetwrap™ and returned to
2 metabolic cages. The systems were removed after 24 hours and the sites
3 were thoroughly washed and marked. Photos and skin evaluations were
4 taken at 2, 24, and 48 hours post-removal and were assessed according to
5 the method of Draize et al. Urine was collected daily for 7 days and analyzed
6 for radioactive content by scintillation counting. The fluoxetine flux was
7 calculated from the urinary excretion data and was corrected by the percent
8 urinary elimination following intracardiac administration of fluoxetine. The
9 results, represented as an average for each formulation tested, are listed in
10 Table 4.

11
12
13 **TABLE 4**

14
15 PII v. flux for various fluoxetine base/acetate formulations

	Fluoxetine	% Fluoxetine (wt/vol) expressed as base	Fluoxetine flux ($\mu\text{g}/\text{cm}^2 \cdot \text{hr}$)	PII
Gel A	0.15 M base	4.6	50.8	6.8
Gel B	0.075 M base	2.3	12.2	3.3
Gel C	0.0375 M base	1.16	5.0	1.7
Gel D	0.328 M acetate	10.1	10.5	1.0
Gel E	0.164 M acetate	5.1	3.6	0.7
Gel F	0.082 M acetate	2.5	2.4	0.3
Gel G	none	0	-	0.3

16
17
18 **EXAMPLE 5**

19 The drug/permeation enhancer reservoirs were prepared by mixing
20 ethylene vinyl acetate having a vinyl acetate content of 40 percent ("EVA 40",
21 USI Chemicals, Illinois), with fluoxetine acetate, hydrocortisone base (HC),
22 GML, and a cosolvent comprising lauryl lactate (LL), dodecyl acetate (DA),
23 or methyl laurate (ML) in a "Brabender" type mixer as set forth in Table 5.
24 After blending, the mixture was calendered into a 6 mil. thick film. The film
25 was then laminated to a 1 mil. unsiliconized polyethylene backing on one
26 side. The composition of the drug reservoirs is shown in Table 5.

TABLE 5

Drug/Permeation Enhancer Reservoir Composition (weight percent).

Sample #	Formulation	Weight Percent
1	fluoxetine acetate/EVA/HC/GML/ML	33/47/5/10/5
2	fluoxetine acetate/EVA/HC/GML/DA	33/47/5/10/5
3	fluoxetine acetate/EVA/HC/GML/LL	33/47/5/10/5
4	fluoxetine acetate/EVA/HC	33/62/5
5 (control)	fluoxetine base/EVA	33/67

Circular pieces of human epidermis were placed with stratum corneum facing up. The release liner of the laminate was removed and the fluoxetine releasing side of the system was centered over the stratum corneum side of the epidermis which had been blotted dry just prior to use. The edges of epidermis were then folded around the system so that none of the system edge was exposed to the receptor solution. This assembly was then mounted on a Teflon® holder of a release rate rod using nylon mesh and metal string. A known volume of receptor solution (0.001 M H₃PO₄) was then placed in a test tube and was equilibrated at 35°C. The test tube was placed in a water bath and maintained at 35°C. The Teflon rod with system and epidermis attached was then reciprocated within the test tube by attaching the rod to a motor which caused constant vertical mixing.

At given time intervals, the entire receptor solution was removed from the test tubes and replaced with an equal volume of fresh receptor solutions previously equilibrated at 35°C. The receptor solutions are stored in capped vials at 4 °C until assayed for fluoxetine content by HPLC. From the drug concentration and the volume of the receptor solutions, the area of permeation and the time interval, the flux of the drug through the epidermis was calculated as follows: (drug concentration X volume of receptor)/(area x time) = flux (μg/cm² · hr). The *in vitro* flux of fluoxetine acetate through epidermis at 35 °C is shown in Figure 8. The *in vitro* flux of hydrocortisone through epidermis at 35 °C is shown in Figure 9.

EXAMPLE 6

Drug reservoirs containing fluoxetine acetate, fluoxetine hydrochloride, or fluoxetine maleate were prepared according to the procedure set forth in Example 5. An adhesive layer was laminated to some of the drug reservoir laminates. The laminate formulations are set forth in Table 6. The acrylate adhesive used was a 2 mil layer of Acrylate #73-9259 (National Starch, Bridgewater, NJ). The PIB was a mixture of 90 wt% low molecular weight PIB (MW 35,000) and 10 wt% high molecular weight PIB (MW 1,200,000) with a 1 mil thickness.

TABLE 6

Drug/Permeation Enhancer Reservoir Composition (weight percent).

Sample #	Formulation	Adhesive	Weight %
1	fluoxetine acetate/EVA/HC	acrylate	33/62/5
2	fluoxetine acetate/EVA	acrylate	33/67
3	fluoxetine acetate/EVA/HC	PIB	33/62/5
4	fluoxetine acetate/EVA	PIB	33/67
5	fluoxetine hydrochloride/EVA/GML/DA/HC	acrylate	33/47/10/5/5
6	fluoxetine hydrochloride/EVA/GML/DA	acrylate	33/52/10/5
7	fluoxetine maleate/EVA/GML/DA/HC	none	33/47/10/5/5
8	fluoxetine maleate/EVA/GML/DA	none	33/52/10/5

Skin fluxes were obtained using the procedure set forth in Example 5. Average skin fluxes (average of 2 skins) over a 72 hour period are given in Table 7. Additionally, skin irritation was measured in a three day wear study conducted on hairless guinea pigs. Irritation was observed at 1/2 hour, 24 hours, and 48 hours after removal of the systems. Primary irritation index (PII) scores were determined using the Draize et al. method and are given in Table 7.

TABLE 7

Average Skin Flux and Primary Irritation Index Scores

Sample	Average Flux ($\mu\text{g}/\text{cm}^2 \cdot \text{hr}$)	PII Score
1	12	1.4
2	13	3.1
3	10	4.4
4	18	5.9
5	8	4.3
6	9	4.5
7	19	1.6
8	17	2.4

EXAMPLE 7

A pharmacokinetic study was conducted on beagels (n=6) to observe fluoxetine and norfluoxetine plasma levels. 60 cm² systems containing the formulation identified as sample 1 of Example 6 were prepared according to the procedure set forth in Example 5. One patch was applied for a 72 hour period to each of the 6 beagels at a site which had been cleaned and shaved prior to application of the system. Blood samples were collected predose, 4, 8, 12, 16, 24, 30, 38, 48, 54, 62, and 72 hours after system application, and at 6, 12, 24, 36, 48, 72, and 96 hours after system removal. The heparinized plasma samples were frozen and sent to Simbec Research Limited, So. Wales, UK for fluoxetine and norfluoxetine assay by gas chromatograph - electron capture detection (GC-ECD). The results are shown in Figure 10, which shows that norfluoxetine levels remained at 96 hours after system removal after a 3 day application.

Having thus generally described our invention and described certain specific embodiments thereof, including the embodiments that applicants consider the best mode of practicing their invention, it should be readily apparent that various modifications to the invention may be made by workers skilled in the art without departing from the scope of this invention which is limited only by the following claims.

1 Wherein, what is claimed is:

2

3 1. A composition of matter for the sustained release of fluoxetine
4 to an individual in need of fluoxetine therapy, the composition comprising an
5 amount of a pharmaceutically acceptable salt of fluoxetine in a carrier
6 effective to permit sustained release of fluoxetine at a therapeutically effective
7 rate within the range of 250 - 3200 $\mu\text{g/hr}$ during an administration period of at
8 least 12 hours in order to administer a therapeutically effective amount of
9 fluoxetine in order to achieve and maintain therapeutic blood or plasma levels
10 throughout a substantial portion of the administration period.

11 2. A composition according to claim 1 wherein the composition is a
12 topical composition and further comprises a permeation enhancing amount of
13 a permeation enhancer.

14 3. A composition according to claim 1 wherein the composition is a
15 topical composition and further comprises an anti-irritant.

16 4. A composition according to claim 3 wherein the salt is fluoxetine
17 acetate or fluoxetine maleate.

18 5. A composition according to claim 3 wherein the anti-irritant
19 comprises a corticosteroid in an amount effective to coadminister said
20 corticosteroid at a rate in excess of $0.1 \mu\text{g/cm}^2 \cdot \text{hr}$ throughout the
21 administration period in order to reduce skin irritation wherein the total
22 amount of corticosteroid delivered is less than 5 mg / 24 hours.

23 6. A composition according to claim 5 wherein the corticosteroid is
24 hydrocortisone.

25 7. A composition according to claim 3 further comprising a
26 permeation enhancer.

27 8. A composition according to claim 7 wherein the permeation
28 enhancer comprises a monoglyceride or mixture of monoglycerides of a fatty
29 acid.

- 1 9. A composition according to claim 8 further comprising a
2 cosolvent selected from the group consisting of fatty acid esters, lactate
3 esters, and alkyl laurates.
- 4 10. A composition according to claim 9 wherein the monoglyceride
5 is glycerol monolaurate and the cosolvent is selected from the group
6 consisting of dodecyl acetate, lauryl lactate, and methyl laurate.
- 7 11. A composition according to claim 7 comprising:
8 (a) 10 to 50 weight % of a pharmaceutically acceptable salt of
9 fluoxetine;
10 (b) 0.01 to 10 weight % of an anti-irritant;
11 (c) 10 to 50 weight % of a permeation enhancer; and
12 (d) 20 to 80 weight % of a polymeric carrier.
- 13 12. A composition according to claim 11 comprising 15 to 40 weight
14 % fluoxetine acetate, 0.1 to 10 weight % hydrocortisone, and 10 to 40 weight
15 % of a permeation enhancer comprising glycerol monolaurate and methyl
16 laurate.
- 17 13. A device for the transdermal administration of fluoxetine at a
18 therapeutically effective rate, comprising:
19 (a) a reservoir comprising an amount of a pharmaceutically
20 acceptable salt of fluoxetine;
21 (b) a backing behind the body contacting-distal surface of
22 the reservoir; and
23 (c) means for maintaining the reservoir in fluoxetine
24 transmitting relation with a body surface or membrane, said device having a
25 surface area defining an area of fluoxetine delivery of less than about 60 cm²,
26 wherein a therapeutically effective amount of fluoxetine is delivered at a
27 therapeutically effective rate within 250 - 3200 µg/hr during an administration
28 period of at least 12 hours in order to achieve and maintain therapeutic blood
29 or plasma levels throughout a substantial portion of the administration period.

1 14. A device according to claim 13 wherein the salt comprises
2 fluoxetine acetate or fluoxetine maleate.

3 15. A device according to claim 13 wherein the reservoir further
4 comprises an anti-irritant.

5 16. A device according to claim 15 wherein the anti-irritant
6 comprises a corticosteroid in an amount effective to coadminister said
7 corticosteroid at a rate in excess of $0.1 \mu\text{g}/\text{cm}^2 \cdot \text{hr}$ throughout the
8 administration period in order to reduce skin irritation wherein the total
9 amount of corticosteroid delivered is less than 5 mg / 24 hours.

10 17. A device according to claim 16 wherein the corticosteroid is
11 hydrocortisone.

12 18. A device according to claim 15 further comprising a permeation
13 enhancer.

14 19. A device according to claim 18 wherein the permeation
15 enhancer comprises a monoglyceride or mixture of monoglycerides of a fatty
16 acid.

17 20. A device according to claim 19 further comprising a cosolvent
18 elected from the group consisting of fatty acid esters, lactate esters, and alkyl
19 laurates.

20 21. A device according to claim 20 wherein the monoglyceride is
21 glycerol monolaurate and the cosolvent is selected from the group consisting
22 of dodecyl acetate, lauryl lactate, and methyl laurate.

23 22. A device according to claim 18 wherein the reservoir comprises:

24 (a) 10 to 50 weight % of a pharmaceutically acceptable salt of
25 fluoxetine;

26 (b) 0.01 to 10 weight % of an anti-irritant;

27 (c) 10 - 50 weight % of a permeation enhancer; and

28 (d) 20 to 80 weight % polymeric carrier.

1 23. A device according to claim 22 comprising 15 to 40 weight %
2 fluoxetine acetate, 0.1 to 10 weight % hydrocortisone, and 10 to 40 weight %
3 of a permeation enhancer comprising glycerol monolaurate and methyl
4 laurate.

5 24. A device for the transdermal administration of fluoxetine at a
6 therapeutically effective rate, comprising:

7 (a) a first reservoir comprising an amount of a
8 pharmaceutically acceptable salt of fluoxetine;

9 (b) a second reservoir comprising an excess of fluoxetine
10 salt at or below saturation when in equilibrium with the first reservoir;

11 (c) a rate-controlling membrane between the first reservoir
12 and the second reservoir;

13 (d) a backing behind the body contacting-distal surface of
14 the second reservoir; and

15 (e) means for maintaining the first and second reservoirs in
16 fluoxetine -transmitting relation with a body surface or membrane, said device
17 having a surface area defining an area of fluoxetine delivery of less than
18 about 60 cm², wherein a therapeutically effective amount of fluoxetine is
19 delivered at a therapeutically effective rate within 250 -3200 µg/hr during an
20 administration period of at least 12 hours in order to provide therapeutic blood
21 or plasma levels.

22 25. A device according to claim 24 wherein the salt is fluoxetine
23 acetate or fluoxetine maleate.

24 26. A device according to claim 24 wherein the first reservoir further
25 comprises an anti-irritant.

26 27. A device according to claim 26 wherein the anti-irritant
27 comprises a corticosteroid in an amount effective to coadminister said
28 corticosteroid at a rate in excess of 0.1 µg/cm² · hr throughout the
29 administration period in order to reduce skin irritation wherein the total
30 amount of corticosteroid delivered is less than 5 mg / 24 hours .

1 28. A device according to claim 27 wherein the corticosteroid is
2 hydrocortisone.

3 29. A device according to claim 26 wherein the first reservoir further
4 comprises a permeation enhancing amount of a permeation enhancer.

5 30. A device according to claim 29 wherein the permeation
6 enhancer comprises a monoglyceride or mixture of monoglycerides of a fatty
7 acid.

8 31. A device according to claim 30 further comprising a cosolvent
9 selected from the group consisting of fatty acid esters, lactate esters, and
10 alkyl laurates.

11 32. A device according to claim 31 wherein the monoglyceride is
12 glycerol monolaurate and the cosolvent is selected from the group consisting
13 of dodecyl acetate, lauryl lactate, and methyl laurate.

14 33. A device according to claim 29 wherein the first reservoir
15 comprises 15 to 40 weight % fluoxetine acetate, 0.1 to 10 weight %
16 hydrocortisone, and 10 to 40 weight % of a permeation enhancer comprising
17 glycerol monolaurate and methyl laurate.

18 34. A method for the transdermal administration of a drug having a
19 half-life of greater than about 24 hours, comprising:

20 a) administering the drug to an area of skin in a carrier
21 effective to permit sustained release of the drug at a therapeutically effective
22 rate through the skin during a first predetermined period of time in order to
23 provide therapeutic blood or plasma levels of the drug;

24 b) removing the drug and carrier from the area of skin for a
25 second predetermined period of time of at least 20 hours wherein no
26 additional drug is applied to the skin during the second predetermined time
27 period;

28 c) repeating steps a) and b) for as long as drug therapy is
29 desired wherein therapeutic blood or plasma levels of the drug are achieved
30 during said first predetermined time period and maintained during said

1 second predetermined period and continue to be maintained for as long as
2 therapy is continued.

3 35. A method according to claim 34 wherein the drug is
4 administered by a transdermal delivery device.

5 36. A method according to claim 35 wherein the first predetermined
6 period is from about 24 - 168 hours.

7 37. A method according to claim 36 wherein the first predetermined
8 period is about 48 - 120 hours.

9 38. A method according to claim 37 wherein the second
10 predetermined period is about 30 - 90 hours.

11 39. A method according to claim 38 wherein the drug is fluoxetine
12 or norfluoxetine.

13 40. A method according to claim 39 wherein the drug is a
14 pharmaceutically acceptable salt of fluoxetine and is administered at a rate
15 within the range of 250 - 3200 $\mu\text{g/hr}$.

16 41. A method according to claim 40 wherein the pharmaceutically
17 acceptable salt of fluoxetine is administered at a rate within the range of 400 -
18 1200 $\mu\text{g/hr}$.

19 42. A method according to claim 35 further comprising
20 simultaneously coadministering an anti-irritant.

21 43. A method according to claim 42 wherein the anti-irritant
22 comprises a corticosteroid and is administered at a flux of at least 0.1 $\mu\text{g/cm}^2$
23 hr and the total amount of corticosteroid delivered is less than 5 mg / 24
24 hours.

25 44. A method according to claim 43 wherein the corticosteroid is
26 hydrocortisone.

27 45. A method according to claim 42 further comprising
28 simultaneously coadministering a permeation enhancer.

29 46. A method according to claim 45 wherein the permeation
30 enhancer comprises glycerol monolaurate and methyl laurate.

- 1 47. A method according to claim 46 wherein the drug is fluoxetine
- 2 or norfluoxetine and the drug, anti-irritant, and permeation enhancer are
- 3 administered from a single transdermal delivery device.

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FIG. 1

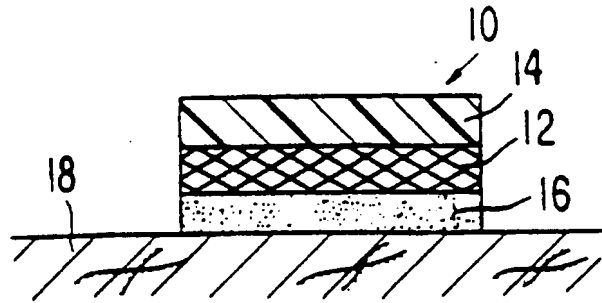


FIG. 2

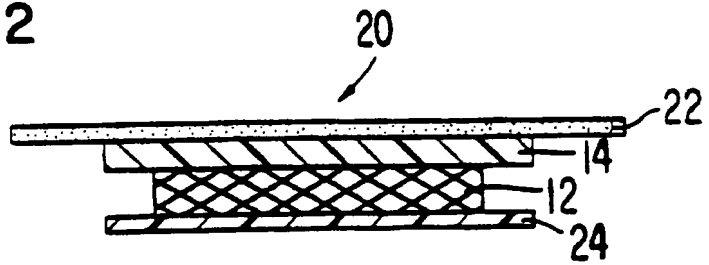


FIG. 3

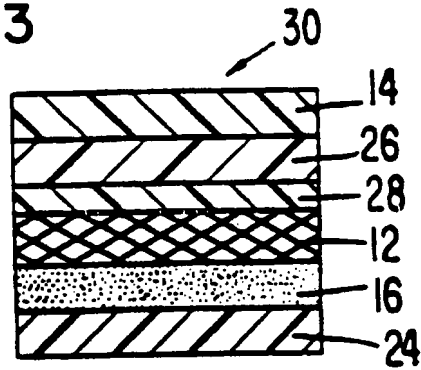
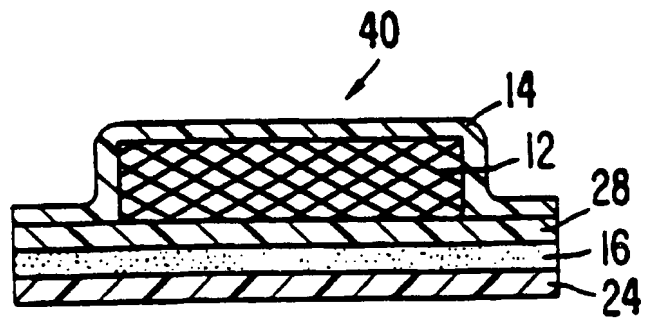


FIG. 4



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FIG. 5

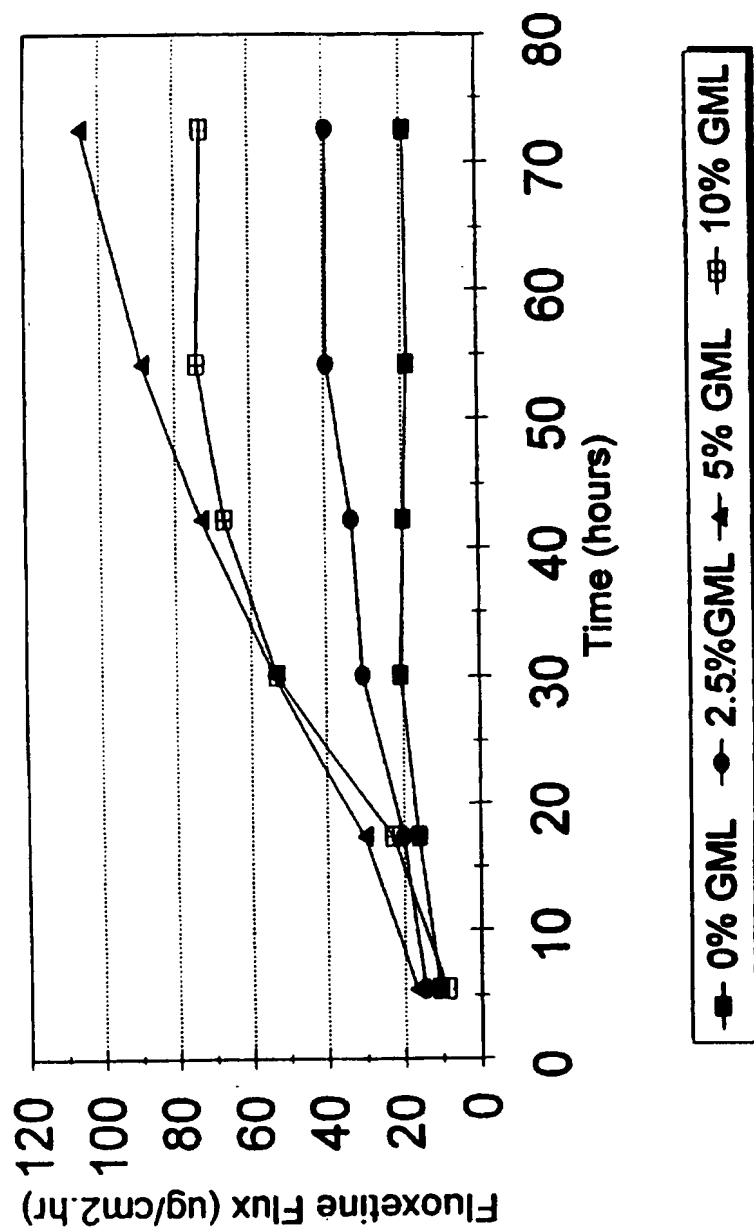


FIG. 6

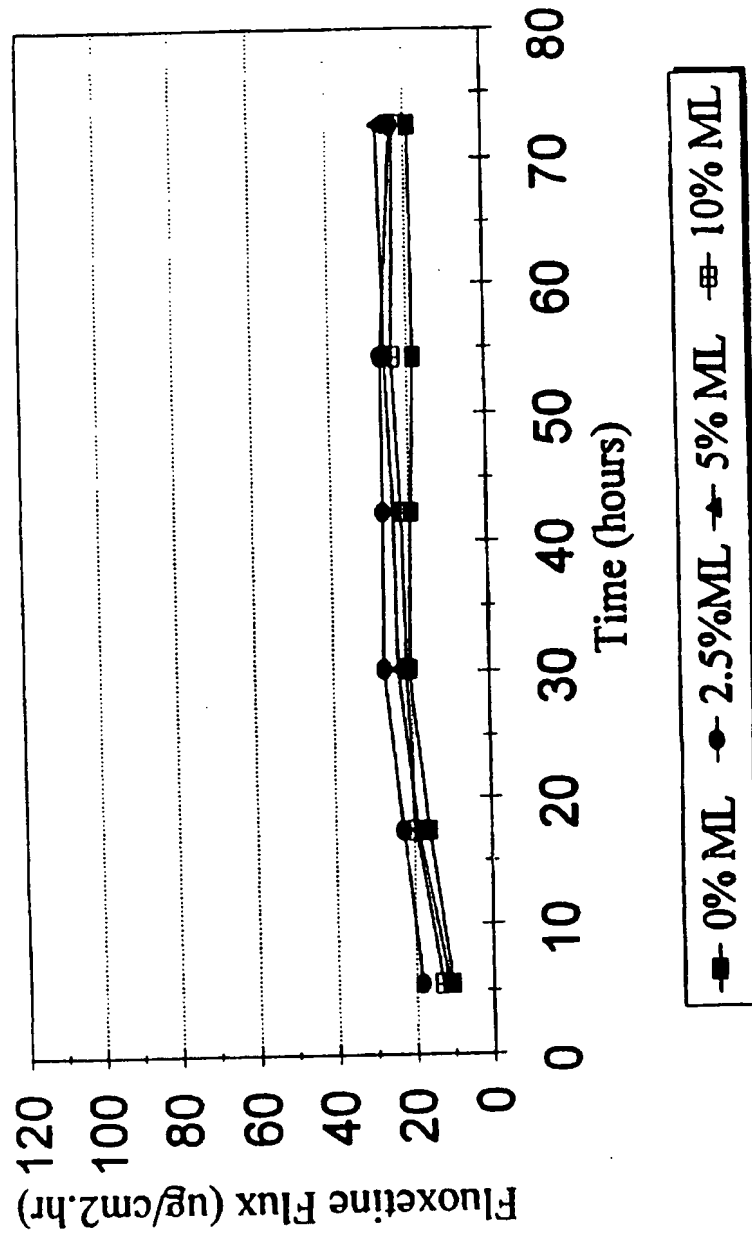
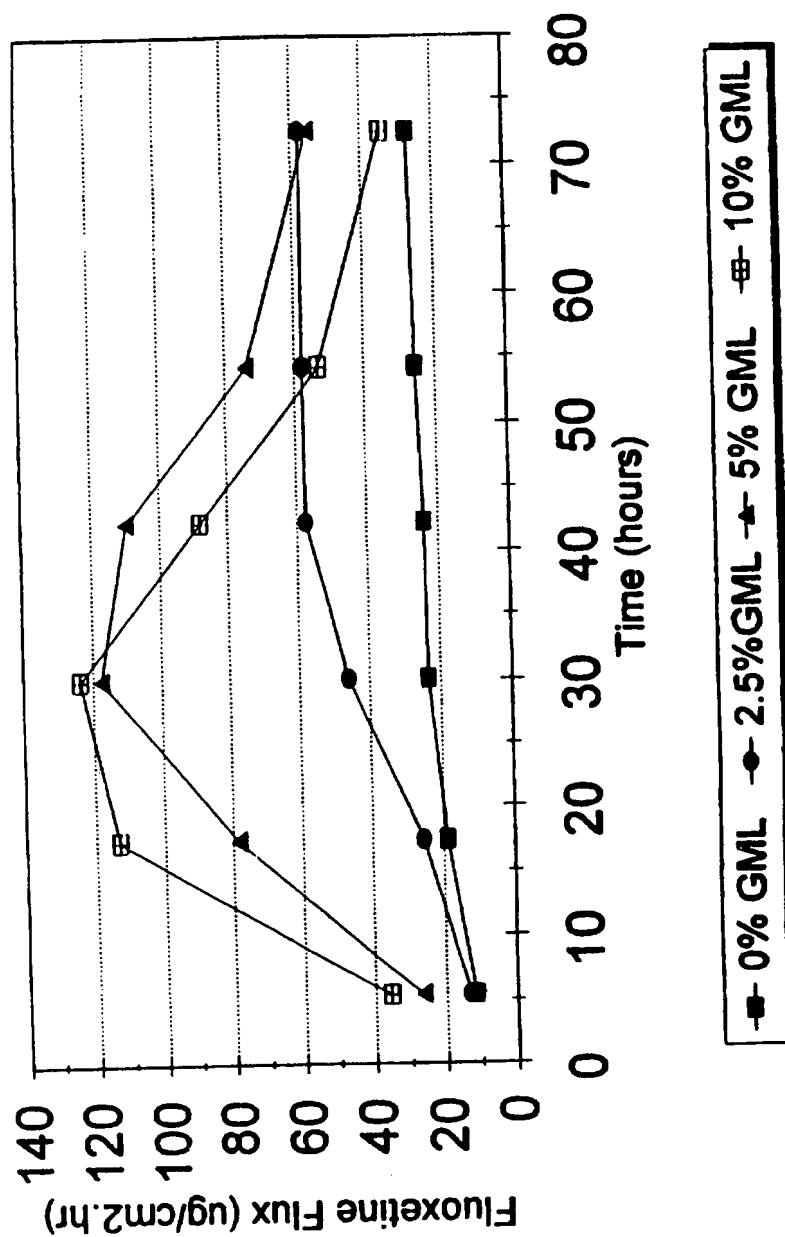
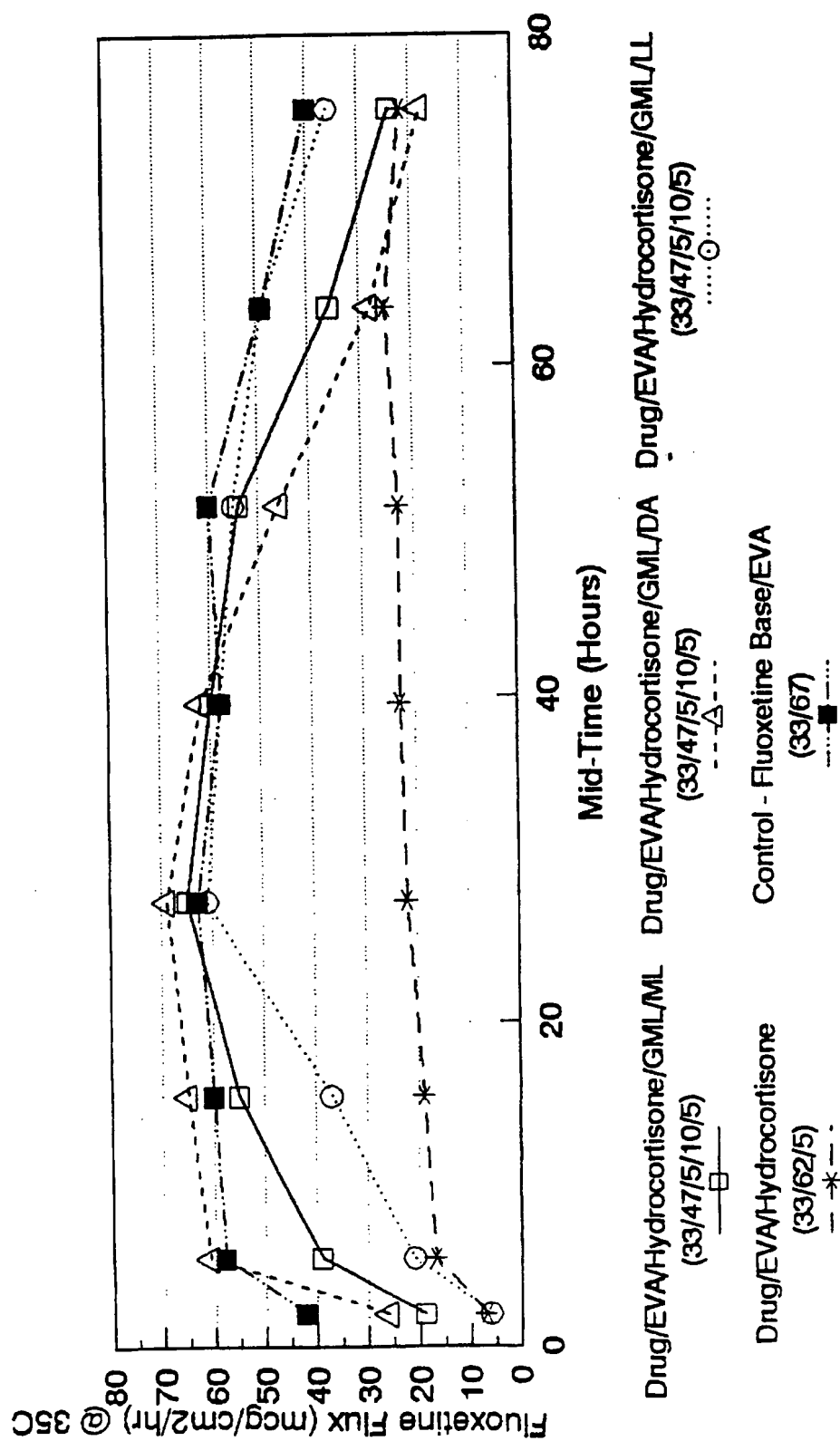


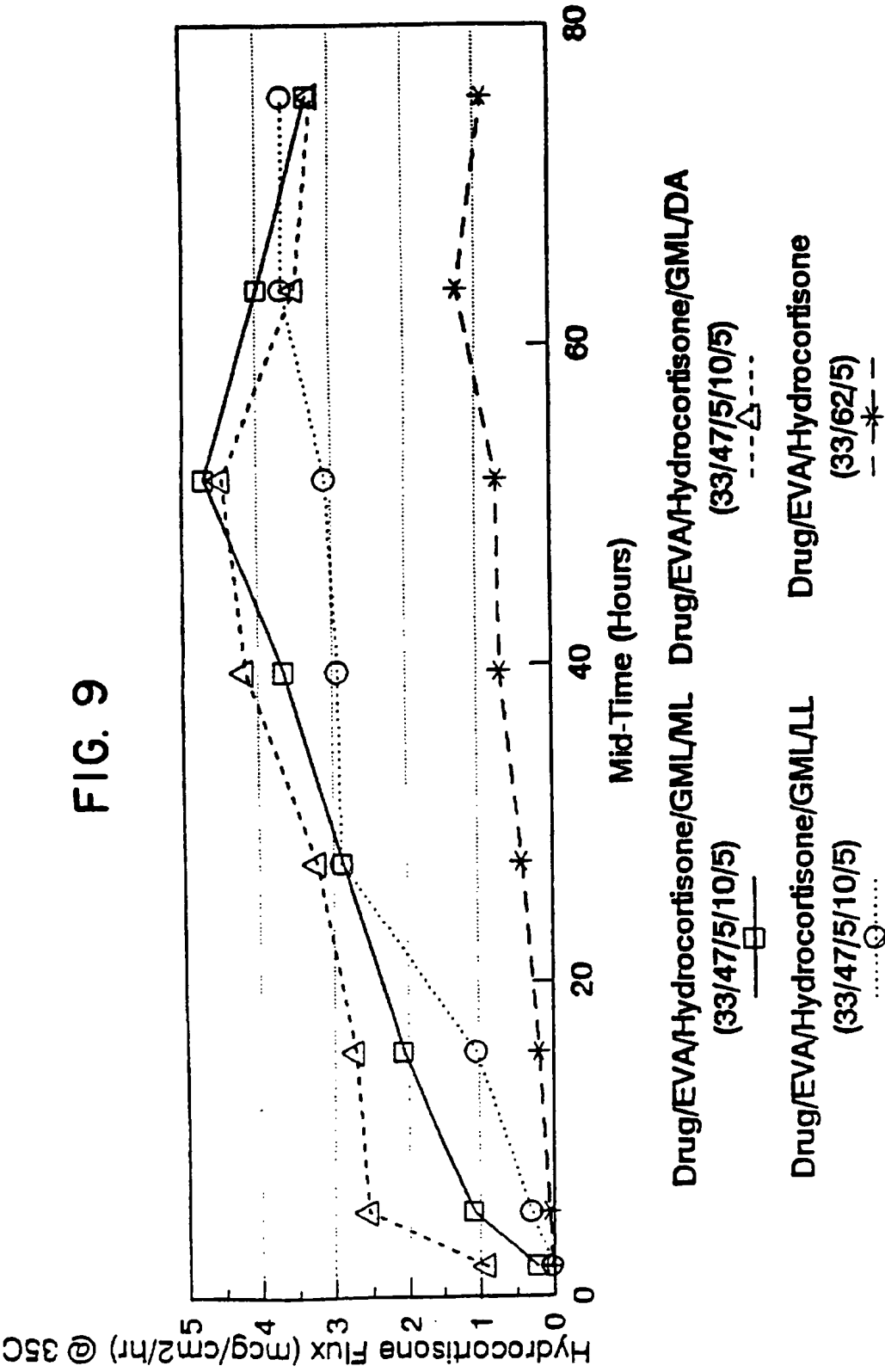
FIG. 7



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FIG. 8





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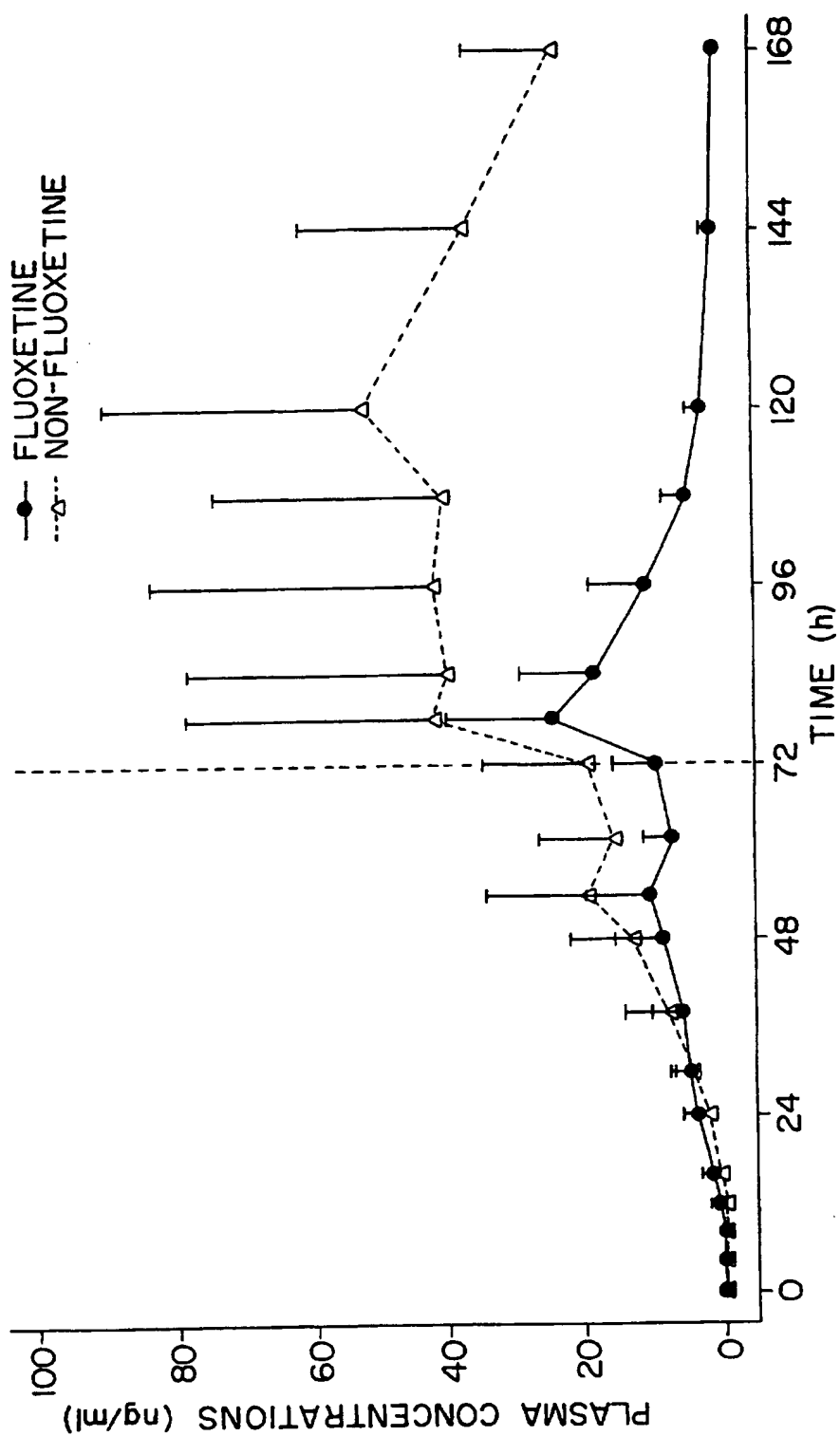


FIG. 10